

**REMARKS**

The October 21, 2003 Official Action and references cited therein have been carefully reviewed. In light of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of the application are respectfully requested.

The Examiner has maintained the rejection of claims 1-18 under 35 U.S.C. §112 first paragraph, asserting that the specification allegedly fails to enable the full scope of the claims. It is the Examiner's position that it would require undue experimentation to determine all compounds which meet the functional limitations recited in the claims.

The Examiner has also maintained the rejection of claims 1-19 under 35 U.S.C. §103(a) as allegedly unpatentable over US Patents 5,972,995, and 6,329,422, both to Fischer et al. It is the Examiner's position that the differences between the instant claims and the teachings of the '995 and '422 patent represent optimization of a result effective variable, and therefore are obvious.

The foregoing constitutes the entirety of the objections and rejections raised in the October 21, 2003 Official Action. In light of the present claim amendments and the following remarks, each of the above-noted rejections under 35 U.S.C. §§ 112, first paragraph, and 103 is respectfully traversed.

**THE CLAIMS ARE FULLY ENABLED BY THE DISCLOSURE IN THE SPECIFICATION**

The Examiner has maintained the rejection of claims 1-18 under 35 U.S.C. §112 first paragraph, asserting that the specification fails to enable the full scope of the

claims. It is the Examiner's position that the functional language in the claims represent a critical limitation, and allegedly there is insufficient guidance, direction, or working examples as to how to obtain, identify, or make the compounds of the invention. Therefore, in the Examiner's opinion, it would require undue experimentation to determine all compounds which meet the functional limitations recited in the claims. The Examiner does indicate that the claims are enabled for compounds described in the specification.

Applicants again submit that it would not require undue experimentation to practice the claimed invention.

See MPEP 2164.06:

"The quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." In re Colianni, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976))."

Specifically, applicants submit that as set forth in the previous response, there is extensive guidance in the specification and the prior art for identifying compounds

which meet the limitations of the claims, and that such compounds may be identified through routine experimentation.

First, it is well established that cystic fibrosis is often characterized by decreased trafficking of a CFTR polypeptide and/or a deceased chloride ion transport. The instant specification describes this at page 3, line 36 over to page 4, line 9; page 16, line 9 over to page 17, line 23; and page 23, lines 9-27. Further, there are numerous compounds which are known to be useful for improving CFTR polypeptide trafficking to the cell surface, or for improving chloride ion transport at the cell surface. These compounds are described throughout the specification, such as at page 19, line 12 over to page 20, line 8, and in the examples. Additionally, at column 8, lines 10-29, US Patent 6,329,422 describes numerous flavones and isoflavones, for enhancing chloride transport, and various assays for testing this effect. Finally, it is routine to test how a particular compound affects CFTR polypeptide trafficking to the cell surface, or chloride ion transport at the cell surface. Various screening methods that can be utilized are detailed throughout the specification. See for example page 22, lines 12-31.

Thus extensive guidance for identifying compounds encompassed by the claims is provided in the specification and the prior art. Further, it would only require routine experimentation to test for the compounds of the invention, using these teachings. Therefore, one must conclude that the disclosure does provide sufficient information for practice of the invention with regard to compounds which enhance the trafficking of a mutant CFTR polypeptide to the surface of an epithelial cell, or

increase the chloride ion transport activity of a mutant CFTR polypeptide at the surface of an epithelial cell.

However, without acquiescing to the Examiner's position, and solely in the interest of expediting prosecution, applicants have amended the claims to recite the compounds to be administered. Specifically, the features of claim 19, which was not rejected for inadequate enablement, have been included in claims 1 and 14, thereby, fully enabling the methods. Accordingly, applicants request withdrawal of this rejection.

**CLAIMS 1-19 AS AMENDED ARE PATENTABLE OVER US PATENTS**

**5,972,995 AND 6,329,422 TO FISCHER ET AL.**

The Examiner has also maintained the rejection of claims 1-19 under 35 U.S.C. §103(a) as allegedly unpatentable over US Patents 5,972,995, and 6,329,422, both to Fischer et al.

The Examiner acknowledges that the Fischer patents do not teach the chronic intermittent treatment schedule of the instant invention. However, the Examiner maintains that utilizing the chronic intermittent treatment schedule as defined in the specification is obvious, because optimization of a result effective variable is considered within the skill of the artisan. The Examiner also indicates that applicants must provide evidence to support any unexpected results.

Again, applicants agree that the Fischer et al. patents do not teach or suggest the specialized, novel chronic intermittent treatment protocol which is critical to the practice of the instant invention. Applicants further submit that the instant treatment is not obvious over Fischer for two reasons:

- (1) First, the chronic intermittent schedule of the instant invention provides an unexpected therapeutic

effect, as evidenced by Wright et al., *Physiol. Genomics* (October 28, 2003).

(2) Second, the Fischer et al. patents teach away from the chronic intermittent schedule of the instant invention.

At the outset, applicants wish to note that the Examiner's citation of the definition of "chronic intermittent dosage schedule" from page 17 of the specification was incomplete. The full definition recites "As used herein, the term 'chronic intermittent treatment' refers to repeated treatment with a compound of a duration wherein the benefit of the treatment is maintained/maximized throughout the duration of the treatment, and treatments are separated by periods of sufficient duration such that repeated treatment does not lessen the benefit of the treatment." Further, this definition is followed by an extensive exemplary dosage protocol, which includes periods in which no compound is administered.

Thus it is clear from the definition that a chronic intermittent treatment schedule requires periods in which compounds are not administered to the patient, in order to prevent tolerance to that compound. Further, all of the claims explicitly recite that the compositions of the invention are administered on a chronic intermittent treatment schedule, so that tolerance is not induced. This concept is not addressed or suggested by Fischer et al., and further would not be obvious in view of Fischer et al.

See MPEP 2144.05 III, which states:

"The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant

must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range." In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

In the instant case, the criticality of the claimed dosage schedule pertains to maintaining the therapeutic efficacy of cystic fibrosis treatment. It is known in the art, and disclosed at pages 8 and 17 of the specification, that chronic administration of CF treatments can lead to induction of tolerance and reduced therapeutic efficacy. The present inventors have found that administration of cystic fibrosis treatments in a chronic intermittent schedule reduces this tolerance. This finding is supported by Wright et al., submitted herewith. This research article describes the effects of the administration of 4-phenylbutyrate (PBA) on gene expression profiles in epithelial cells in order to provides further insight into the action of PBA at the molecular level. At pages 17-18, Wright et al. teach that administration in a "pulsed" dosage schedule" could be used to prevent tolerance, and improve treatment efficacy. Notably, Wright et al. was published after the filing date of the present application. Accordingly, the claims of the instant invention are not obvious in view of Fischer et al., because the instant claims produce an unexpected enhanced therapeutic effect, as evidenced by Wright et al.

Second, while the instant invention specifies that the treatments be separated by a period of time, the Fischer et al. patents require daily administration of compounds. If a reference teaches away from an

invention, that reference cannot be used as a basis for an obviousness rejection.

**MPEP 2144.05 III:** A *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. In re Geisler, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997)

The chronic intermittent schedule of the invention is disclosed at pages 8-9 of the specification, and preferably includes one to two weeks of administration, followed by a two to four week period in which the patient is not treated. Further, the instantly claimed protocol includes concurrent and staggered administration of the drugs of the invention. Such a treatment schedule prevents the undesirable induction of tolerance to the compounds, thereby providing an improved protocol for the beneficial treatment of cystic fibrosis.

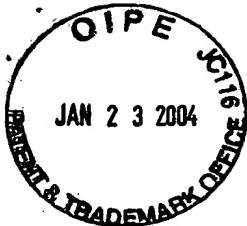
Neither of the Fischer patents provides any significant guidance regarding a specific or particular administration protocol. Instead, an extremely broad dosage range (2-30 g/daily) is given. Further, there is no mention or suggestion in the Fischer et al. patents to discontinue administration for periods of time, as is critical to the instantly claimed chronic treatment protocol. The skilled artisan would reasonably conclude from the Fischer et al. patents that the periods without drug administration, which are part of the instantly claimed chronic intermittent administration schedule, would inhibit treatment efficacy. Since the methods of Fischer et al. require daily administration of therapeutic compounds, while the instant invention requires intermittent administration, it is clear these

patents teach away from the methods of the instant invention, which is further evidence of non-obviousness.

Therefore, in light of the clear differences in treatment protocols, and the above-mentioned unexpected results, claims 1-19 are patentable over US Patents 5,792,995 and 6,329,422 to Fischer et al. Accordingly, Applicants respectfully request that the rejection of claims 1-19 under 35 U.S.C. §103 be withdrawn. At minimum, claims 16 and 17, which specify specific protocols for a chronic intermittent treatment schedule are not obvious in view of the Fischer patents.

#### CONCLUSION

It is respectfully requested that the amendments presented herewith be entered in this application, since the amendments are primarily formal, rather than substantive in nature. This amendment is believed to clearly place the pending claims in condition for allowance. In any event, the claims as presently amended are believed to eliminate certain issues and better define other issues which would be raised on appeal, should an appeal be necessary in this case.

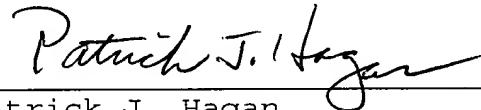


In view of the amendments and remarks presented herewith, it is respectfully urged that the rejections set forth in the October 21, 2003 Official Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,

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